

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61L 31/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/21309</b> <b>(43) International Publication Date:</b> 29 September 1994 (29.09.94)
<b>(21) International Application Number:</b> PCT/BE94/00024 <b>(22) International Filing Date:</b> 24 March 1994 (24.03.94)  <b>(30) Priority Data:</b> 9300285 24 March 1993 (24.03.93) BE  <b>(71) Applicant (for all designated States except US):</b> N.V. D.S.B. [BE/BE]; Meirbrug 1, Bus 2, B-2000 Antwerp (BE).	<b>(81) Designated States:</b> AU, BG, BR, CA, CN, CZ, HU, JP, NZ, PL, RO, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> POLYURETHANE-COATED INTRAVASCULAR PROSTHESES (STENTS) FOR THE TREATMENT OF BLOOD VESSEL STENOSIS  <b>(57) Abstract</b>  A new method to treat blood vessel stenosis using endovascular prostheses which are coated with amphiphilic polyurethanes to which medicines can be coupled. By coating endovascular prosthesis with amphiphilic polyurethanes, we have succeeded in significantly improving the bio- and bloodcompatibility of endovascular prostheses. These amphiphilic polyurethanes have the property, when implanted in human or animal tissue and blood vessels, of remaining stable and seeming not to provoke an inflammatory reaction. Furthermore it is possible to incorporate medicines in these polymers which, after implantation of the polymers, are slowly released at the location of the place of implantation. This system can further reduce the thrombogenicity of the prostheses coated with the polyurethanes and inhibit the rejection against these prostheses.		

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POLYURETHANE-COATED INTRAVASCULAR PROTHESES (STENTS) FOR THE  
5 TREATMENT OF BLOOD VESSEL STENOSES. A new method to treat  
blood vessel stenoses by means of endovascular protheses  
which are coated with amphiphilic polyurethanes to which  
medicines can be coupled.

## 10 DESCRIPTION

Treatment of blood vessel stenoses by means of a balloon  
catheter is a popular method. Last year, more than  
15 6,000 patients with coronary heart disease were treated by  
this method in our country. The problem with this method is  
on the one hand the danger that a tear occurs during the  
blowing up of the balloon whereby the blood vessel can close  
and thus cause an acute myocardial infarction, on the other  
20 hand it is well documented that this treatment method is  
accompanied by a frequent restenosis of the treated blood  
vessel within 6 months of the treatment. To solve this  
problems, medicines were tested in order to prevent the  
restenosis and furthermore new devices were developed.  
25 One of these new methods consist of placing a metal  
intravascular prothesis (stent) at the level of the vessel  
stenosis. This method is very efficient for treating vessel  
tears which can occur during balloon dilatation. The problems  
with this metallic stents however are that they have proven  
30 to be thrombogenic and can cause an acute thrombotic  
occlusion of the treated blood vessel. On the other hand, it  
appeared that through the implantation of a metal stent in a  
blood vessel, the body can react with an inflammatory  
reaction whereby restenosis within the stent can occur.  
35 By covering these endovascular protheses with amphiphilic  
polyurethanes, we succeeded in significantly limiting both  
the problem of thrombogenicity as well as the problem of  
reactive hyperproliferative response.  
Amphiphilic polyurethanes were synthesized starting from  
40 amphiphilic polyester diols on the basis of ethylene oxide  
and propylene oxide. By reaction with a diisocyanate and a  
chain lengthener (butanediol), a thermoplastic polyurethane  
is finally obtained. By the appropriate choice of a) the  
polyesterdiol, especially the proportion of  
45 ethyleneoxide/propyleneoxide, and b) the molecular weight  
of the diol, the bio- and blood compatibility can be  
optimized. Furthermore the kind of sterilisation of  
polyurethane-coated devices turned out to be very critical.  
We used certain amounts of gamma radiation which resulted in  
50 the formation of further crossbridging of the polymer leading  
to a more stable and more elastic polymer which is critical  
during the stent deployment. The resulting polymers turned  
out to be very stable when implanted in human or animal  
tissues or blood vessels. Furthermore they did not provoke  
55 any inflammatory reaction.  
Furthermore we were able to load these polyurethanes with  
medicines, which were released slowly at the polymer  
implantation side. These medicines are used to further  
decrease the thrombogenicity of the stents (heparin, hirudin,  
60 streptokinase, urokinase, tpa and other anticoagulants) and

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to inhibit the inflammatory reaction caused by the stent  
(corticosteroids, antimitotics, angiopeptin and other  
10 antiinflammatory drugs.) Using methylprednisolone loaded  
polyurethane coated stents we were able to block totally the  
stent restenosis in a pig coronary model.

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#### APPLICATION POSSIBILITIES OF THE SYSTEM

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1. Treatment of blood vessel stenosis in humans and animals.

2. Treatment of complications occurring during other  
treatment methods of blood vessel stenosis.

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3. Treatment of complications occurring during diagnostic  
procedures.

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4. Coating of prosteses, wires, and catheters introduced for  
medical purposes.

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## CLAIMS

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By coating endovascular prostheses with amphiphilic polyurethanes, we have developed an efficient method to treat blood vessel stenosis. This method proved to considerably limit the thrombogenicity as well as the

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rejection against endovascular prostheses so that this method signifies an important step forward in the treatment of blood vessel stenosis.

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 518 704 (SCIMED LIFE SYSTEMS) 16 December 1992 see claims 3,4,9-13 ---	1
Y	WO,A,87 04935 (FISCHEL R.E.) 27 August 1987 see claim 11 ---	1
Y	WO,A,92 15286 (NOVA PHARMACEUTICAL) 17 September 1992 see page 1, line 9 - line 21; claims 1,2,5; example 5 ---	1
P,A	EP,A,0 566 245 (MEDTRONIC) 20 October 1993 see claims 1,3,5,28 --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

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Date of the actual completion of the international search

1 June 1994

Date of mailing of the international search report

08.06.94

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 371 686 (YAMAMOTO N.) 1 February 1983 see column 1, line 6 - line 22 -----	1

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
"Remark: Although claim 1 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the product."
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0518704	16-12-92	JP-A- 5200048	10-08-93
WO-A-8704935	27-08-87	DE-A- 3786721	02-09-93
		EP-A, B 0257091	02-03-88
		EP-A- 0556940	25-08-93
		US-A- 4768507	06-09-88
WO-A-9215286	17-09-92	AU-A- 1579092	06-10-92
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		JP-B- 58008700	17-02-83